

Progression of coronary atherosclerosis

Clues to pathogenesis from serial coronary arteriography

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SUMMARY Fifty two patients with coronary artery disease underwent repeat coronary arteriographic studies separated by 2-108 (mean 51) months of medical treatment. The results were compared and correlated with symptoms to determine the nature of the progression of coronary atherosclerosis. The condition appeared to progress episodically in the proximal segments of the coronary arteries and in relation to the abrupt development of new symptoms or acute coronary events such as unstable angina or myocardial infarction. Thirty four of 105 (33%) of the pre-existing stenoses showed evidence of progression. Progression to total occlusion was uncommon (13) except for stenoses >90% (six out of 18). New lesions frequently occurred (37) in previously normal segments of the arteries; most of these were stenoses >90% (13) or total occlusions (12). Rapid progression of a mild lesion and new lesions occurred in the form of smooth intimal protrusions into the arterial lumen. Intimal haemorrhages are the likely explanation for these intimal encroachments and also for the episodic nature of the progression of coronary artery disease. Coronary atherosclerosis does not progress gradually in a linear fashion, and local anatomical factors appear to play a dominant role in the natural history.

Present knowledge of the natural history of atherosclerosis is based primarily on pathological examination of the lesions at necropsy. Histopathological examination provides unequivocal information on their form and composition. Nevertheless, the lesions can be examined only at one point in their natural history and the events leading up to that point are based mainly on imaginative reconstruction.¹ Arteriography allows the disease to be studied during life and offers the advantage of recording the evolution of lesions by serial studies on the same patient. In the 1970s several studies²⁻⁶ attempted to examine the progression of coronary atherosclerosis by serial angiography. These were heterogeneous studies which included symptomatic and asymptomatic patients with and without coronary artery disease. Some important points emerged from them even though the conclusions

reached were conflicting. Only one study⁵ examined the behaviour of individual lesions after a mean follow up period of 26 months.

In the past decade the widespread application of coronary bypass surgery, and more recently coronary angioplasty, have altered the natural history of coronary artery disease. These interventions have also prevented systematic studies of the natural progression of the disease process. The present report is based on the analysis of serial coronary arteriograms of 52 patients medically treated for periods of up to nine years. Careful observation of the morphology of progression, particularly that of the new lesions, and correlation with the patients' symptoms provided important clues to the natural history of coronary atherosclerosis.

Patients and methods

The clinical and arteriographic records of all patients with coronary artery disease who had undergone at least two arteriographic examinations without surgical intervention between October 1974 and September

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1983 were reviewed. During this period 1424 patients underwent cardiac catheterisation, 993 of whom had coronary artery disease. Fifty two patients fulfilled the criteria for inclusion in the study; 47 men and five women ranging from 28 to 62 (mean 49) years in age at the time of the first study. Twenty nine patients had one vessel disease, 16 two vessel disease, and seven three vessel disease. At this time either the disease was considered not to be severe enough to warrant surgery, or the patient elected medical treatment, or surgery was offered but refused. In 51 patients the indication for recatheterisation was the development of new symptoms or persistent symptoms. One patient was electively re-examined because of the unexpected disappearance of symptoms. The interval between the arteriographic studies ranged from 2 to 108 (mean 51) months. Nineteen of these patients underwent coronary bypass surgery after the second study, but only three were subsequently re-examined because of symptoms. In these three patients, the postoperative follow up studies were included, but the grafted arteries were excluded from analysis.

A careful history was taken before each study. All except five of the angiographic studies were performed by me and recorded on 35 mm cine film at 30 frames/s using a Philip's 6 inch image intensifier. In five patients, one of the two studies was performed in another institution. These five studies were performed on different equipment, but the angiograms were adequate for comparison. Both the coronary arteries were examined in multiple oblique projections after the routine administration of 0.4 mg of sublingual glyceryl trinitrate. Additional sublingual glyceryl trinitrate was given when necessary, and on one occasion 0.2 mg of intracoronary glyceryl trinitrate was also used.

Two coronary arteriograms from each patient were simultaneously projected from adjacently placed Tagarno 35 mm projectors and compared. The individual stenoses were measured with calipers and recorded. The individual lesions were graded according to the percentage reduction in luminal diameter: grade 1, <50%, grade 2, 50–69%, grade 3, 70–89%, grade 4, 90–99%, grade 5, 100%. The progression of coronary artery disease was defined as: (a) an increase in pre-existing stenosis by >25%, (b) development of a new lesion >25%, and (c) total occlusion of any vessel not previously totally occluded. Regression was defined as a decrease in stenosis by >25%. Two or more lesions in the same vessel were counted separately.

The arterial segments filling by collaterals were excluded from analysis.

Results

CLINICAL CORRELATIONS

Table 1 shows the time interval between the studies in the 52 patients. Of the total patient population, 45 (87%) showed progression of coronary atherosclerosis, six stable disease, and one regression only. Of the 45 patients with progressive disease, 28 had progression in pre-existing lesions and 27 had new lesions (10 patients showed progression as well as new lesions). All these patients had been re-examined because of an abrupt onset of new symptoms or an acute coronary event such as unstable angina or myocardial infarction. Of the six patients showing stable disease, five had been studied because of persistent symptoms and denied a change in symptoms and one had had a myocardial infarction. One patient who showed regression only had been electively studied because of the unexpected disappearance of symptoms (Fig. 1).

LESIONS

Table 2 shows the distribution of the different grades of severity of the lesions in the first study and their progression as well as the grade of severity of new lesions in the second study. One hundred and twenty nine lesions were found in the first arteriographic study: 108 stenoses and 21 total occlusions. Three of the 21 total occlusions had recanalised by the second study (Figs. 2 and 3), but the criteria for regression were not fulfilled. Of 108 stenoses, 105 were available for comparison in the second study; in three instances the vessel had completely occluded proximal to the lesion. Of the 105 stenoses, 34 (33%) showed progression, 68 remained stable, and three showed true regression (Figs. 1 and 4). Of the 37 new lesions in the second study, 27 occurred in previously normal arteries and 10 in the arteries with lesions elsewhere.

INTERVAL BETWEEN STUDIES AND PROGRESSION OF LESIONS

The mean interval between the studies was similar for new lesions of varying grades of severity and the pre-existing lesions that had remained stable. It was also similar (48 months) for the lesions of <70% which showed progression. The mean interval between studies was significantly shorter (22.5 months) for the

Table 1 *Interval between the two arteriographic studies in 52 patients with coronary artery disease*

<i>Interval (mths):</i>	<i><12</i>	<i>13–24</i>	<i>25–36</i>	<i>37–48</i>	<i>49–60</i>	<i>61–72</i>	<i>73–84</i>	<i>85–96</i>	<i>97–108</i>
No of patients	4	6	11	9	6	4	1	9	2

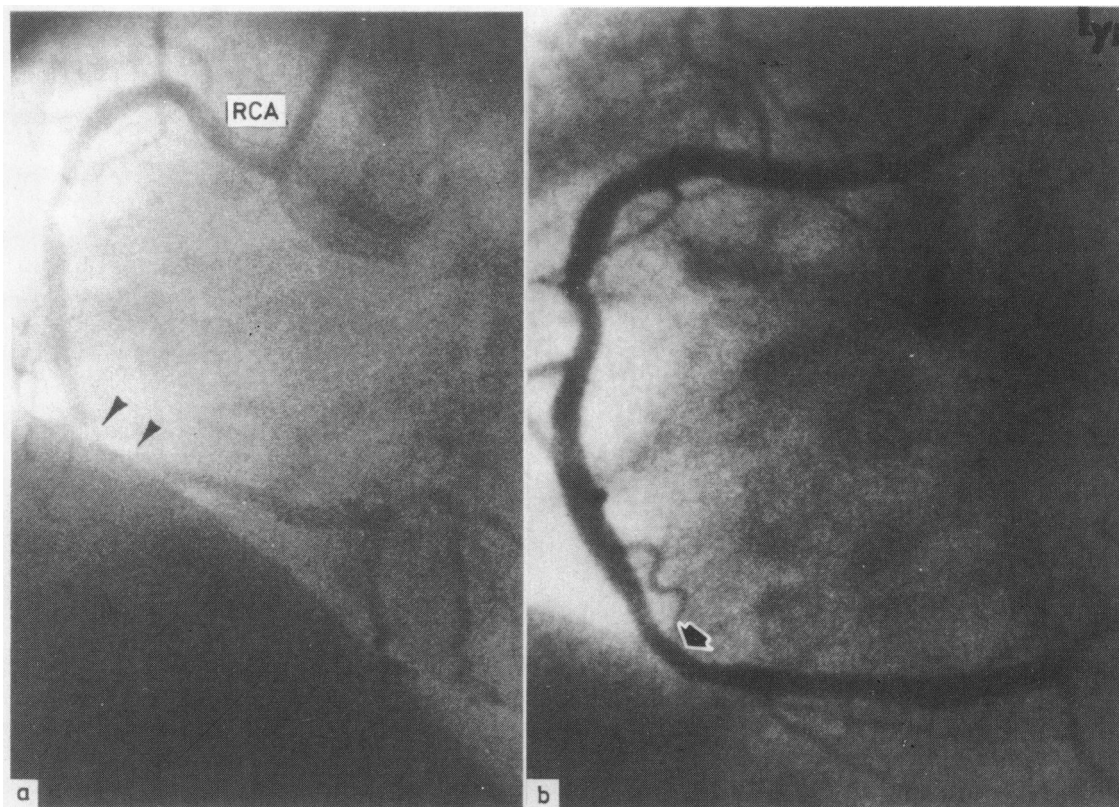


Fig. 1 Coronary arteriograms: (a) shows a right coronary artery (RCA) after recent onset of angina and positive stress test (note subtotal obstruction (arrowheads) and (b) a more magnified image one year later shows only mild intimal thickening at that site (arrow); the patient was asymptomatic with a negative treadmill test.

Table 2 Distribution and behaviour of lesions in 52 patients with coronary artery disease. Figures are numbers of lesions*

	Grade 1 (<50%)	Grade 2 (50–69%)	Grade 3 (70–89%)	Grade 4 (90–99%)	Grade 5 (100%)
Lesions in the first study	33	39	15	18	21
Behaviour of lesions:					
Stable	19	27	12	10	—
Progressed	14 (3)	11 (2)	3 (2)	6 (6)	—
Regressed	0	1	—	2	—
New lesions in the second study	5	3	4	13	12

*Figures within brackets are the number of lesions which progressed to total occlusion.

lesions >70% which progressed to total occlusion. The difference is statistically significant ($p < 0.05$).

Discussion

There are limitations to the visual assessment of the severity of coronary artery stenosis, particularly in view of interobserver differences in arteriographic

interpretation. For the purpose of comparison, however, the simultaneous projection of arteriograms is a better solution than separate analysis by several reviewers. The routine use of glyceryl trinitrate before arteriography reduces the possibility of focal coronary spasm. Hopefully, it produced comparable vasodilatation in the two studies, so minimising the errors of observation. A conservative definition of the progres-

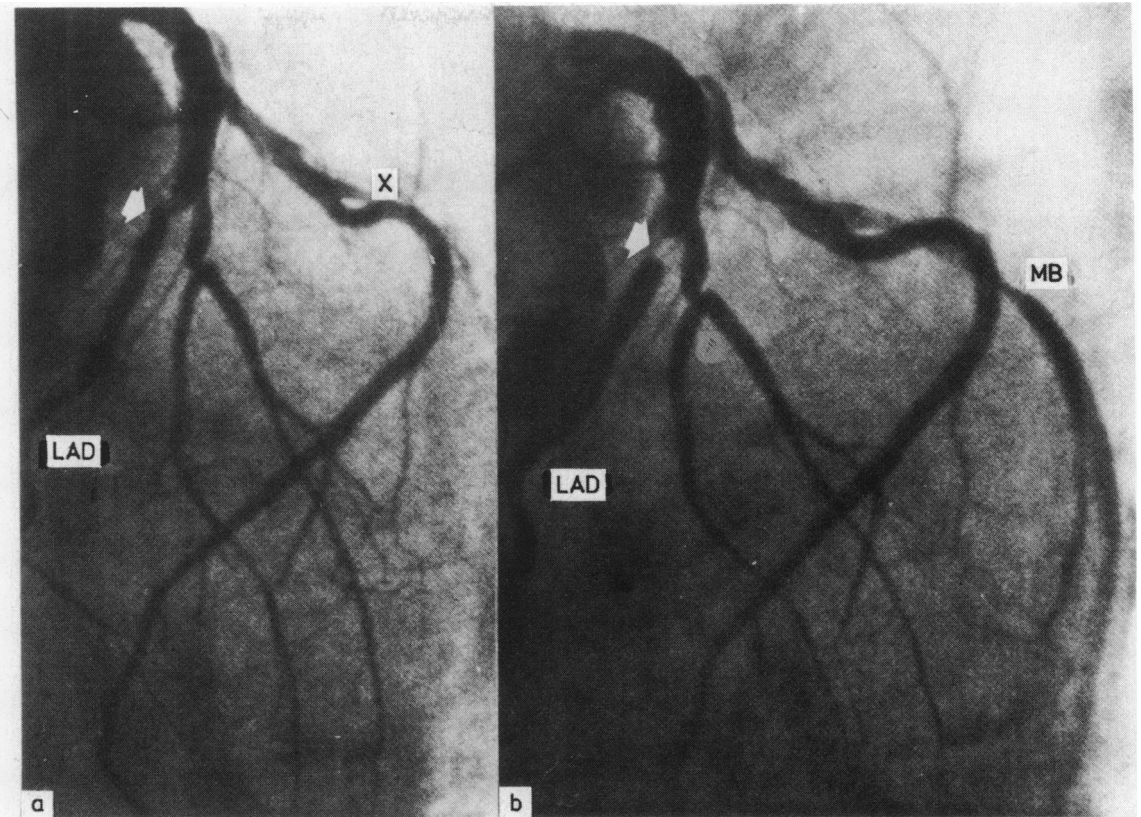


Fig. 2 Coronary arteriograms: (a) shows total occlusion (X) of the marginal branch of left circumflex artery and mild narrowing (arrow) of the proximal left anterior descending artery (LAD); and (b) three years later shows subtotal obstruction (arrow) at the site of old mild narrowing in the left anterior descending artery; the morphology suggests a mural thrombus. The marginal branch (MB) has recanalised.

sion of change in stenosis by 25% is similar to that in other reported series³⁻⁷ and excludes minimal or questionable changes in arteriographic appearance. This retrospective study represents a selected group of symptomatic patients and naturally excludes asymptomatic patients, who are more likely to have stable disease. A few patients who were referred because of persistent rather than a change in symptoms did show stable disease. On the other hand, the patients with an abrupt onset of new symptoms nearly always showed progression. This accords with a recently reported study⁸ showing a high incidence of progression in patients with unstable angina and a low incidence of progression in patients with stable angina.

The manner in which progression occurs is of interest. In this study two thirds of the pre-existing lesions remained stable and only one third showed progression. Progression frequently occurred in the form of

new lesions. These observations are consistent with those of other studies.^{3 5 7 8}

SITE OF LESIONS

Progression occurred in the proximal segments of the coronary arteries, which are well known to have predilection for atherosclerosis.⁹ This is also consistent with other arteriographic studies.^{3 5 7 8} These are the segments of the coronary arteries which are subject to stresses of movement during cardiac systole. Cine coronary arteriography offers special advantages because the arteries can be seen in motion and the stress points identified. The portions of the arteries which are bent, particularly the junctions of moving and fixed parts of the vessels, are especially vulnerable. Favoured sites are (a) the right coronary artery around the origin of the marginal branch, which anchors the artery to the right ventricle (Figs. 4 and 5), (b) the distal right coronary artery before the ter-

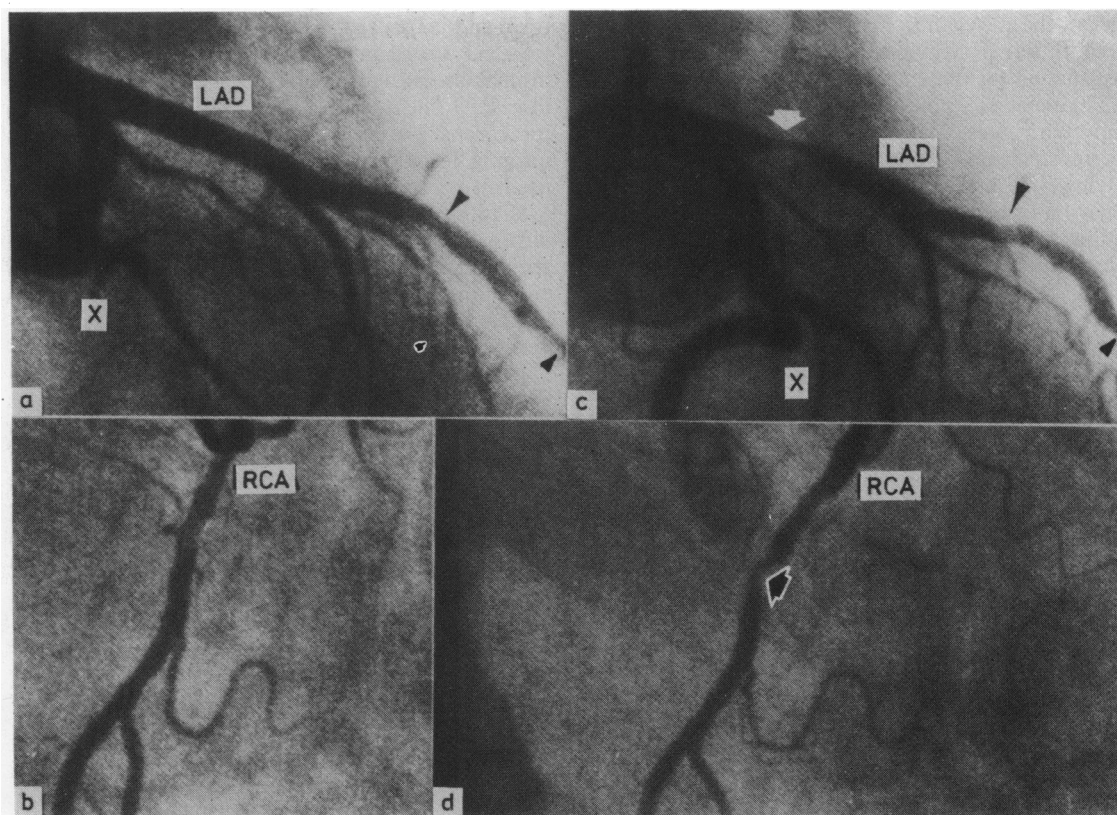


Fig. 3 Coronary arteriograms; (a) shows total occlusion (X) of one subdivision of the marginal branch of the left coronary artery and mild irregularities (arrowheads) in the mid portion of left anterior descending artery (LAD); (b) shows mild irregularities proximally of the right coronary artery (RCA); (c) shows that the mild irregularities in the mid left anterior descending (LAD) artery are unchanged but a new high grade lesion has developed proximally (arrow) (note the asymmetrical but smooth intimal protrusion); the previously occluded branch (X) has recanalised; (d) shows a new asymmetrical intimal protrusion (arrow) in the proximal right coronary artery (RCA).

minal branches, which anchor the artery to the left ventricle (Fig. 6), (c) the lateral circumflex branches just proximal to their intramural course (Figs. 7 and 8), and (d) the left anterior descending artery both above and below the first septal branch, which fixes the artery to the interventricular septum (Figs. 3, 6, and 9). Stress points such as these are known to be favoured sites of lesions in other arteries, such as those of the lower limbs¹⁰ and the internal mammary arteries.¹¹ The local anatomical factors appear to be dominant in the aetiology of atherosclerosis.¹² Any valid theory of atherosclerosis must explain the freedom of certain segments of vessels from disease as well as lesions in the affected segments.

PROBABLE PATHOLOGICAL MECHANISMS

It is clear from this study as well as other reported serial studies³⁻⁷ that coronary artery disease does not

progress linearly. The progression is quite unpredictable, frequently occurring in previously normal sites (Figs. 3-8), and shows little or no correlation with coronary risk factors.^{4,6,7} These observations conflict with the popular theories of genesis and progression of atherosclerosis. It is said that atherosclerosis starts in childhood in the form of "fatty streaks" with gradual maturation into raised fibrolipid plaque by middle age. The frequent occurrence of a high grade new lesion in a previously normal segment of the vessel and the stability of most pre-existing lesions appear to conflict with the idea of a gradual build up of plaque tissue. Gradual progression also occurs and may be due to deposits of fibrin within the substance of the plaques. This does not, however, explain rapidly developing new lesions. Other mechanisms of inception and progression of atherosclerosis may be operative. It is quite likely that the common end

point—the raised fibrolipid lesion—may be reached from different beginnings.¹ Is there a pathogenic explanation for these arteriographic observations?

The detailed studies of Lindbom¹⁰ appear to offer important clues. He performed a large number of antemortem and postmortem arteriographic studies of the lower limb arteries and correlated these with necropsy findings. He was unable to diagnose the diffuse intimal thickening arteriographically but could detect focal intimal thickening of even a slight degree (0.25 mm). The intimal haemorrhages were a frequent cause of intimal protrusions into the lumen. These were of intramural origin and were usually covered by intact endothelium. He explained the rapidly developing intimal protrusions during life by the occurrence of intimal haemorrhages and produced evidence for this by undertaking antemortem and postmortem arteriography in the same patient followed by pathological examination.

Lindbom's observations were not limited to large arteries but included the arteries of the lower leg. The

tibial and peroneal arteries are similar in size and histological structure to the coronary arteries. When intimal disease develops it is similar to coronary artery disease.¹² The extrapolation of Lindbom's findings to the coronary arteries is therefore justified. Modern imaging techniques and the multiple oblique views used in coronary arteriography enable even smaller focal intimal protrusions to be detected. Nevertheless, diffuse intimal thickening is not easily diagnosed arteriographically. It may be discernible in the form of minimal luminal irregularities (Fig. 3) because the intima is practically always irregular when thickened.¹⁰

Even though the present study provides no pathological proof, the morphology of the new lesions in the coronary arteriographic studies accords with Lindbom's observations. A smooth convex bulge into the arterial lumen, sloping to merge with the normal lumen proximally and distally, is the characteristic appearance of intimal haemorrhage. The smooth appearance probably indicates intact endothelium

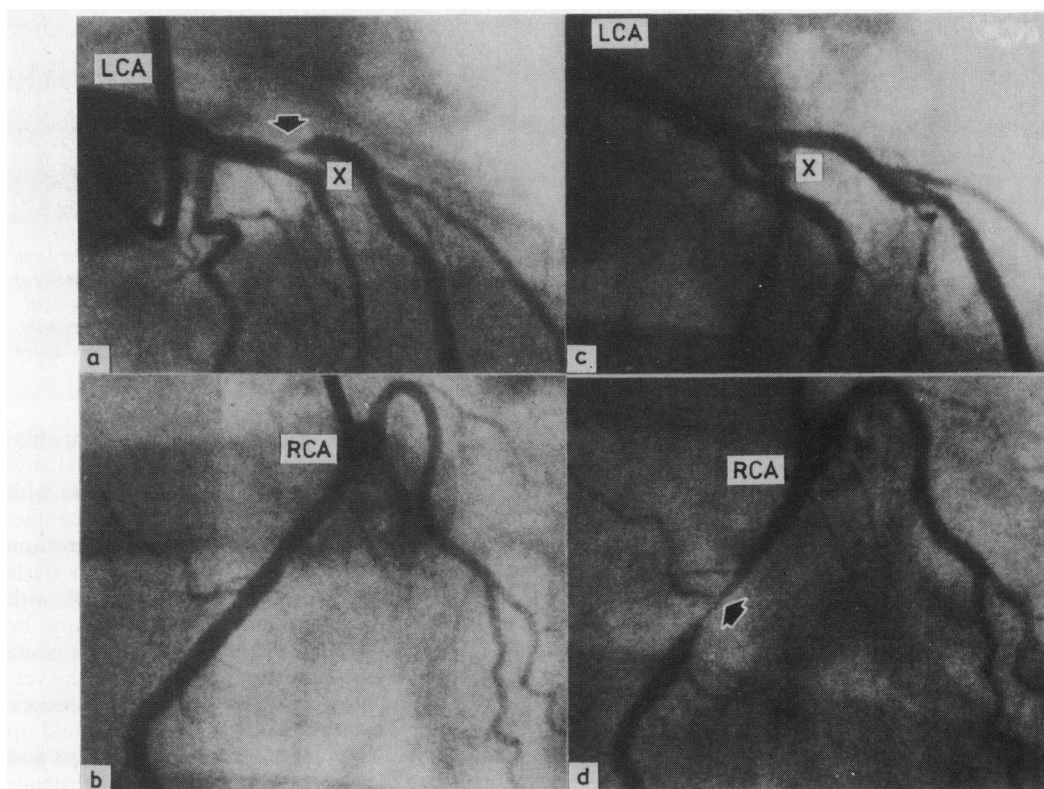


Fig. 4 Coronary arteriograms: (a) shows total occlusion (X) of the left anterior descending artery and a high grade lesion (arrow) in a large intermediate ramus. (b) the right coronary artery (RCA) is essentially normal; three months later, the patient became asymptomatic and discontinued treatment. (c) Six years later the lesion in the intermediate ramus had completely regressed and (d) a new high grade lesion had developed (arrow) in the proximal right coronary artery (RCA). LCA, left coronary artery.

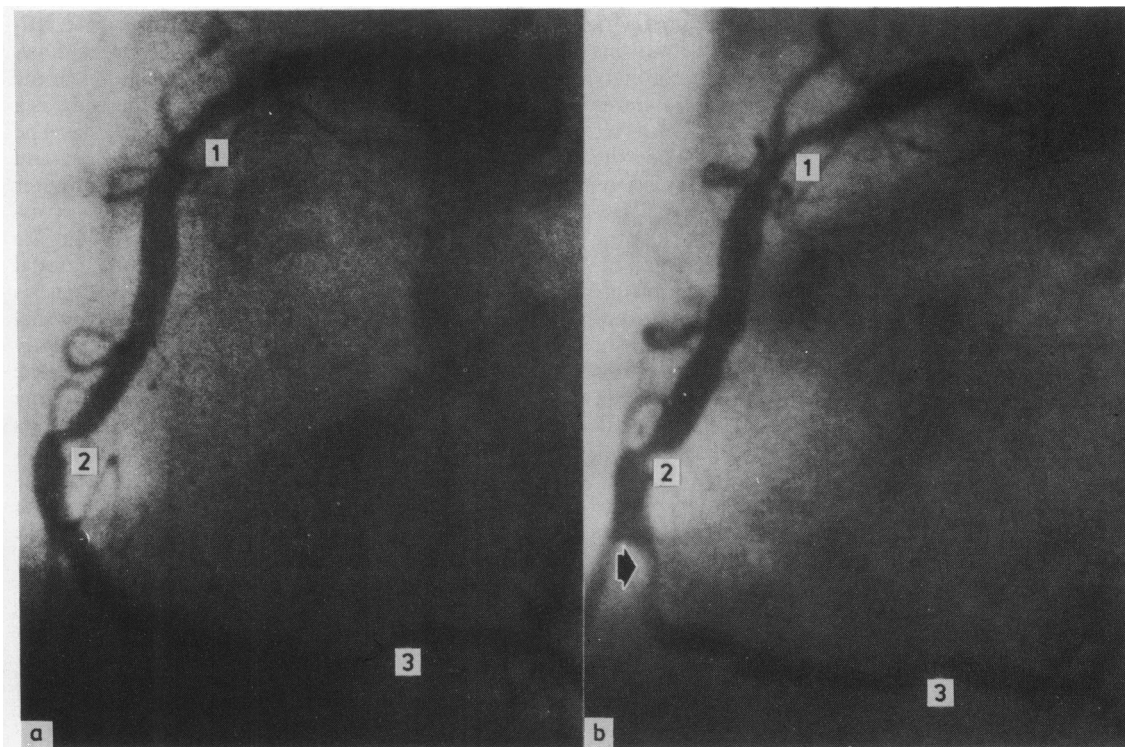


Fig. 5 Coronary arteriograms: (a) shows three lesions of the right coronary artery. (b) Two and a half years later one lesion (1) had progressed but two ((2) and (3)) were unchanged. A new lesion had developed (arrow). Note the asymmetrical but smooth intimal protrusion.

without a surface thrombus. The same characteristic morphology was seen in most of the rapidly progressive mild lesions. At times the latter had the appearance of a filling defect, without sharp margins (Figs. 2 and 9), which I believe represents a mural thrombus. In these cases, studied within a few days of the acute event, delayed clearance of the contrast agent at the filling defect was additional evidence of their thrombotic nature. Incorporation of mural thrombus into the intimal lesion is another important cause of the increase in the dimensions of atherosclerotic lesions.^{13 14} This is probably a frequent mode of progression of the lesions that are already well established. Serial angiographic studies are not very helpful in ascertaining this because the changes in morphology in the second study are difficult to evaluate when significant luminal distortion is already present in the first study. Incorporated mural thrombi may undergo organisation. Fibrin is converted into fibrous tissue and the blood corpuscles into fat droplets¹⁴; a fibro-lipid plaque results, leaving little or no evidence of its true origin. The behaviour of intramural haemorrhages is probably similar to that of "red" thrombi described by Duguid,¹⁴ which organise poorly and

undergo fatty degeneration. Softer lesions may result. Recent experience with coronary angioplasty has indicated that the lesions with an hour glass configuration, associated with the recent onset of symptoms, are most easily compressed by this procedure. The occurrence of intimal haemorrhage may also explain acute occlusion during the procedure as well as frequent restenosis¹⁵ within a few months. Pathological correlations are scanty but support this point of view.¹⁶

In the present study population, there were two instances of notable regression (Figs. 1 and 3). This could be explained by the absorption of haematoma without an appreciable fibrous reaction.

TOTAL OCCLUSIONS

Thrombosis is undoubtedly the final event in all total coronary occlusions except those which are transient. The mechanism that triggers thrombosis is still not well understood. A commonly accepted mechanism is plaque rupture, which in turn is believed to occur owing to attenuation of its fibrous cap.^{17 18} Falk recently studied 103 plaque ruptures in 47 patients dying of coronary artery disease.¹⁸ Intimal haemor-

rhage was present in all cases and was associated with occlusive thrombus in 40. Total occlusion from this mechanism occurred always if pre-existing coronary stenosis was $>95\%$, occurred frequently if stenosis was 90–94%, and was rare if stenosis was $<75\%$. This may explain why in the present study population the total occlusion was frequent only at the site of lesions $>90\%$. This mechanism does not, however, satisfactorily explain the total occlusions that occurred at the sites which were previously found to be arteriographically normal. It is difficult to envisage that a plaque had formed, matured, and undergone degeneration of its fibrous cap in only a few months. The possibility of an acutely developing intimal lesion has to be considered. An intimal tear, erosion, or haemorrhage could have precipitated thrombus formation in these cases.

PROBABLE SOURCE OF INTIMAL HAEMORRHAGES

Intimal haemorrhage is a well known complication of atherosclerosis.^{9 19–22} Contemporary pathologists

tend to trace the origin of these haemorrhages to intimal dissection from the lumen.^{13 17 18} There is, however, another school of thought which believes in the intramural origin of these haemorrhages, arising as a sequel to vascularisation of the intima.^{19 20 23 24} The wall of a medium sized artery derives its oxygen and nutrients from two sources: the adventitia and outer two thirds of the media are supplied by the vasa vasorum while the intima and inner part of the media are supplied by diffusion from the blood in the arterial lumen.^{13 24} The borderline between these two zones is prone to hypoxia by any process that leads to intimal thickening. As intima thickens with age, particularly in the segments of arteries exposed to haemodynamic or mechanical stresses, the deeper parts of the intima may become richly vascularised from the capillaries derived from the vasa vasorum. Attention was first drawn to this phenomenon by Winternitz and coworkers²³ and later supported by Geiringer.²⁴ Recently, Barger *et al* demonstrated cinematographically the

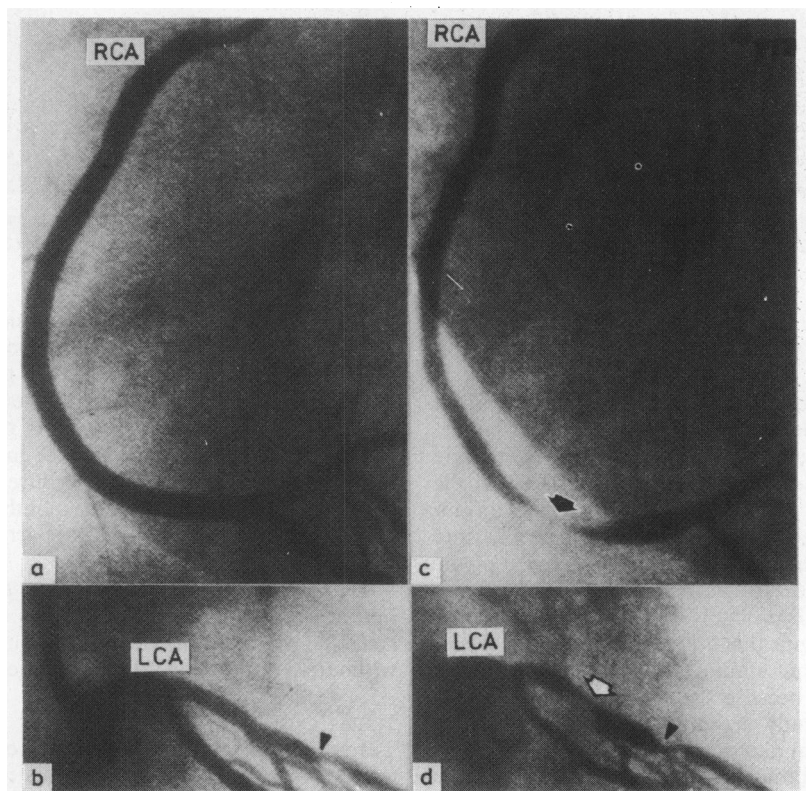


Fig. 6 (a) and (b) Coronary arteriograms performed because of recent onset angina and a positive treadmill test. (a) The right coronary artery (RCA) is normal. (b) A left coronary arteriogram (LCA) shows 60% stenosis (arrowhead) of the left anterior descending artery. The patient became asymptomatic with medical treatment. (c) and (d) Coronary arteriography repeated four years later because of recent onset of severe angina on effort shows that (c) a new subtotal obstruction (arrow) had developed in the distal right coronary artery (RCA) and (d) the moderate stenosis in the mid left anterior descending artery (arrowhead) was essentially unchanged but a new stenosis had developed proximally (open arrow). Note the asymmetrical but smooth intimal protrusion.

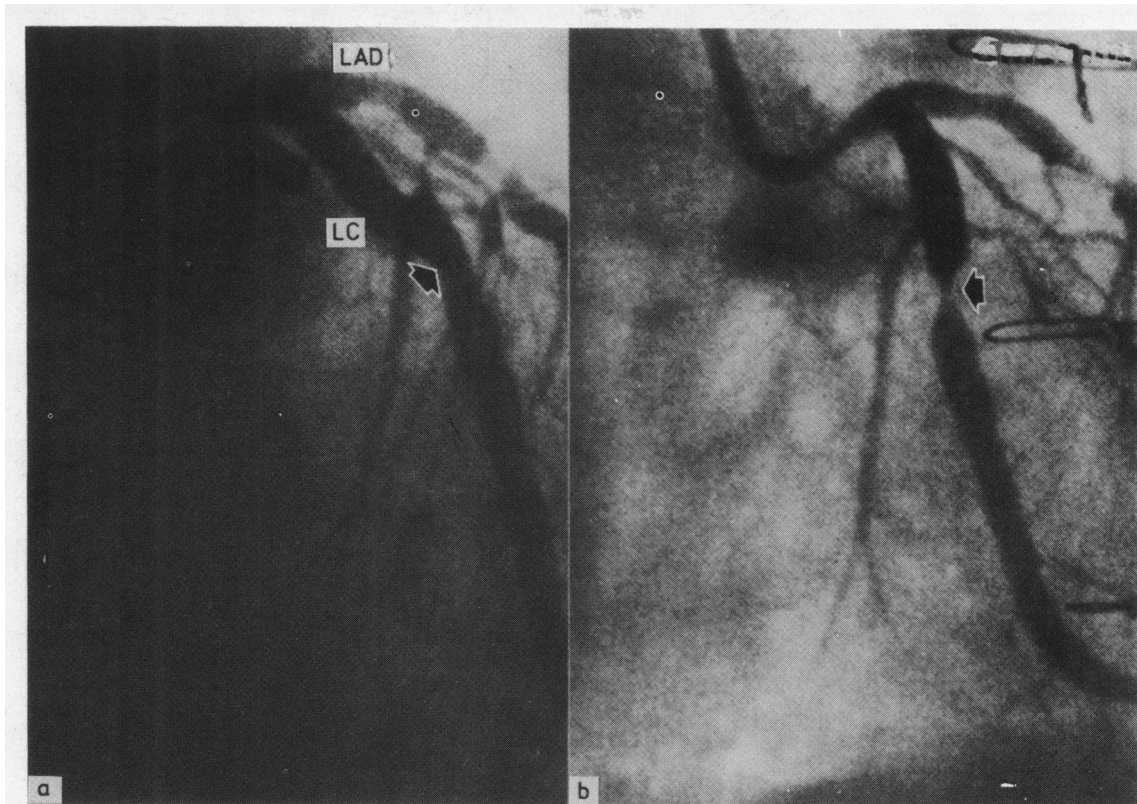


Fig. 7 (a) Left coronary arteriogram in the right anterior oblique projection showing a high grade lesion in the proximal left anterior descending artery (LAD) and an essentially normal left circumflex artery (LC). The arrow denotes the bend in the artery with cardiac systole. The patient underwent bypass grafting to the left anterior descending artery. (b) Six months later a new high grade lesion (arrow) had developed in the circumflex artery at the bend. Note the smooth and symmetrical intimal protrusions.

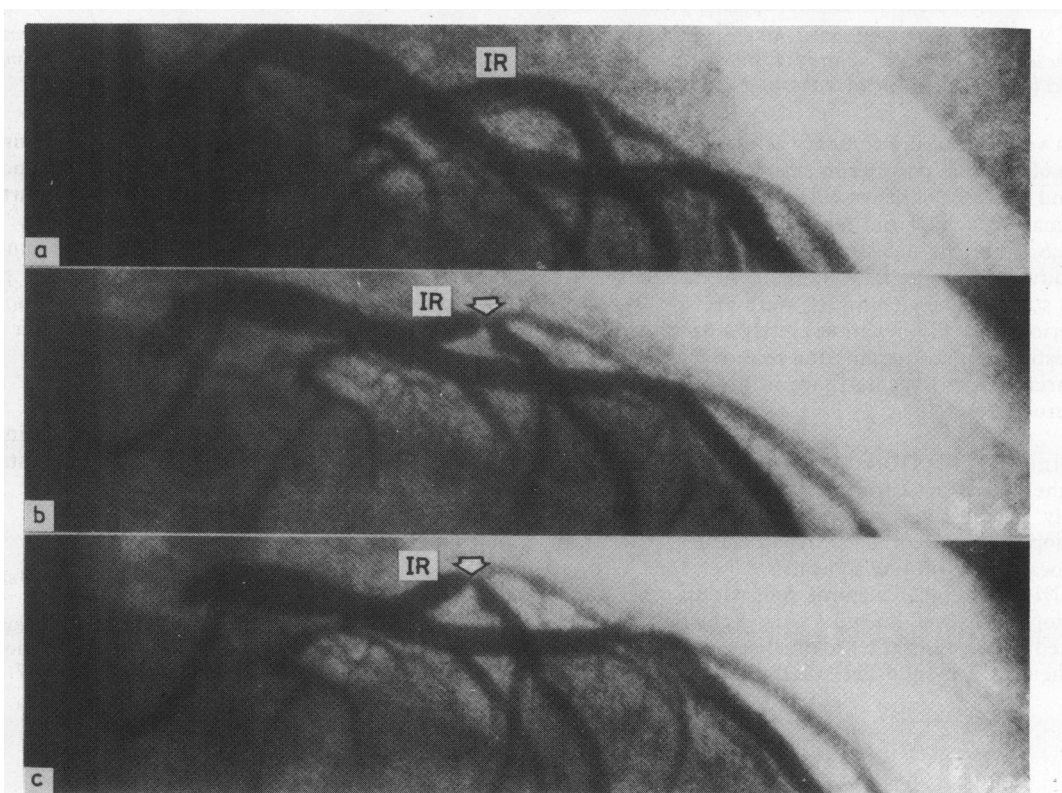


Fig. 8 Left coronary arteriograms showing (a) normal left coronary artery; (b) a high grade lesion (arrow) in the intermediate ramus (IR) eight years later; and (c) a bend in the vessel at the site of the lesion during cardiac systole.

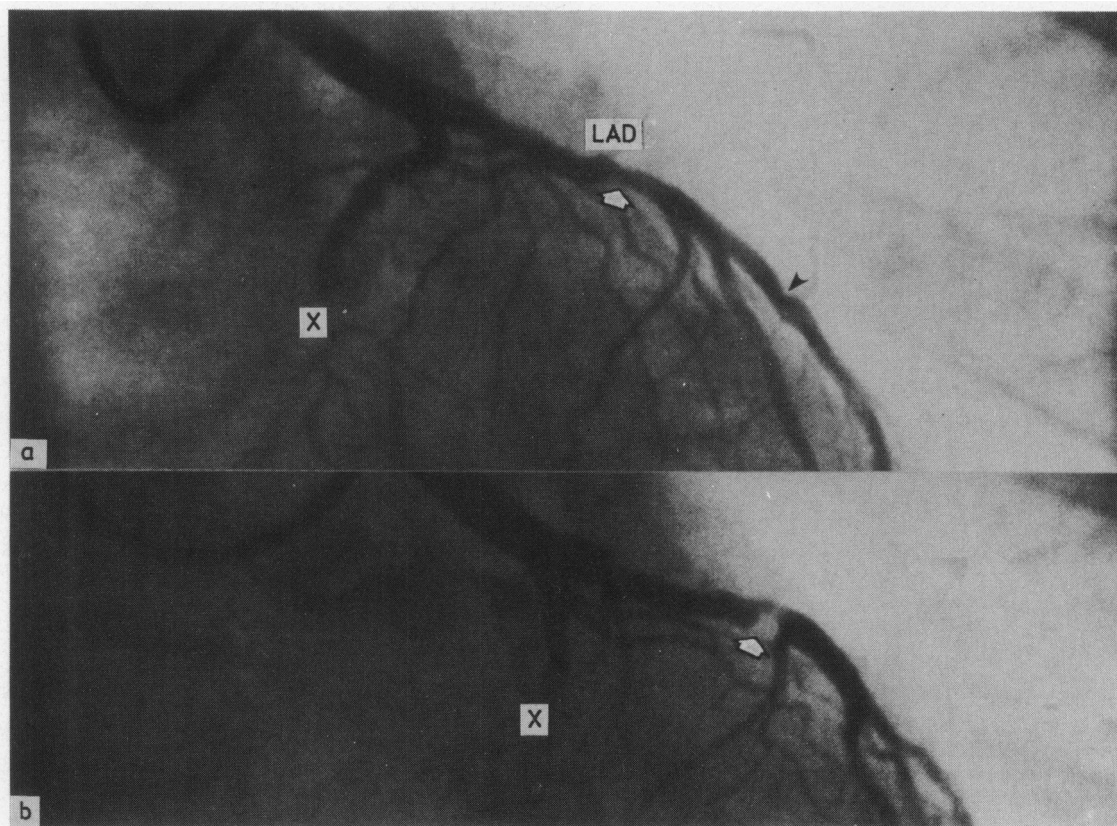


Fig. 9 Left coronary arteriograms. (a) shows total occlusion (X) of the circumflex division and only mild intimal thickening (arrows) of the left anterior descending artery (LAD). (b) One week after recent onset angina (three and a half years later) a high grade filling defect (arrow) had developed at the site of old intimal disease and is probably a mural thrombus.

vasa vasorum of the coronary arteries after the injection of a silicon polymer in cleared human hearts and found evidence of neovascularisation in the regions of intimal thickening and plaque formation.²⁵ Haemorrhages from the neovascularised intima would most readily explain the new intimal protrusions seen in this study at the sites which were previously normal arteriographically. There is clearly a need for further investigations to examine the role of intimal neovascularisation and haemorrhage in the pathogenesis of atherosclerosis.

OTHER IMPLICATIONS OF THE STUDY

In the belief that coronary artery lesions are relentlessly progressive, interventions such as coronary angioplasty and coronary bypass surgery have been advocated "prophylactically"^{15 26} for lesions <60%. The high restenosis rate within a year after angioplasty is well known.¹⁵ Also known is the accelerated occlusion of the proximal coronary lesion after saphenous vein grafting²⁶ and the tendency of the

vein grafts to fail in time.^{27 28} In view of the temporary benefit from these procedures and the demonstrated stability of two thirds of the coronary artery lesions during the follow up period in this study, the wisdom of these prophylactic interventions can be questioned. Coronary atherosclerosis does not progress gradually in a linear fashion, and local anatomical factors appear to play a dominant role in the pathogenesis.

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